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Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis — Source link ⬈

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ORIGINAL ARTICLE

Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis

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ABSTRACT

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BACKGROUND

Nonselective beta-adrenergic blockers decrease portal pressure and prevent variceal hemorrhage. Their effectiveness in preventing varices is unknown.

METHODS

We randomly assigned 213 patients with cirrhosis and portal hypertension (minimal hepatic venous pressure gradient [HVPG] of 6 mm Hg) to receive timolol, a nonselective beta-blocker (108 patients), or placebo (105 patients). The primary end point was the development of gastroesophageal varices or variceal hemorrhage. Endoscopy and HVPG measurements were repeated yearly.

RESULTS

During a median follow-up of 54.9 months, the rate of the primary end point did not differ significantly between the timolol group and the placebo group (39 percent and 40 percent, respectively; P=0.89), nor were there significant differences in the rates of ascites, encephalopathy, liver transplantation, or death. Serious adverse events were more common among patients in the timolol group than among those in the placebo group (18 percent vs. 6 percent, P=0.006). Varices developed less frequently among patients with a baseline HVPG of less than 10 mm Hg and among those in whom the HVPG decreased by more than 10 percent at one year and more frequently among those in whom the HVPG increased by more than 10 percent at one year.

CONCLUSIONS

Nonselective beta-blockers are ineffective in preventing varices in unselected patients with cirrhosis and portal hypertension and are associated with an increased number of adverse events. (ClinicalTrials.gov number, NCT00006398.)

NONSELECTIVE BETA-ADRENERGIC blockers reduce portal pressure through a reduction in portal venous inflow[1,2] as a result of a decrease in cardiac output (β_1-adrenergic blockade) and splanchnic blood flow (β_2-adrenergic blockade). Randomized, controlled trials have demonstrated that nonselective beta-blockers prevent variceal hemorrhage in patients with varices.[3] Decreasing portal pressure at earlier stages may prevent gastroesophageal varices. In fact, an experimental study demonstrated that beta-blockers prevent the development of portosystemic collateral vessels.[4] Therefore, we conducted a study to evaluate the efficacy of nonselective beta-blockers in preventing gastroesophageal varices and to assess whether baseline and sequential measurements of the hepatic venous pressure gradient (HVPG) are useful in predicting the development of varices.

METHODS

The study was an investigator-initiated, randomized, double-blind, placebo-controlled, clinical trial conducted at four sites. The protocol was approved by the institutional review board at each site, and all patients gave written informed consent. Timolol maleate (Blocadren) and placebo were provided by Merck; Merck did not participate in any other aspect of the study, including study design, data analysis, and manuscript preparation.

PATIENTS

Patients were enrolled between August 1993 and March 1999 and followed until September 2002. Eligible patients had cirrhosis and portal hypertension, as defined by an HVPG of at least 6 mm Hg; did not have gastroesophageal varices; and were older than 18 years and younger than 75 years of age. The diagnosis of cirrhosis was either biopsy-proven or clinically suspected and confirmed by the finding of an HVPG of 10 mm Hg or greater. The absence of gastroesophageal varices was determined unanimously at endoscopy by two staff endoscopists who were present during the entire procedure and who evaluated the procedure independently. Exclusion criteria included ascites requiring diuretics, hepatocellular carcinoma, splenic- or portal-vein thrombosis, concurrent illnesses expected to decrease life expectancy to less than one year, the use of any drug or procedure affecting splanchnic hemodynamics or portal pressure, primary biliary cirrhosis or primary sclerosing cholangitis, con-traindications to beta-blocker therapy, pregnancy, or alcohol intake during the dose-titration phase.

Of 780 patients screened for varices, 490 (63 percent) had none. Of these 490 patients, 213 (43 percent) were included in the study. The remaining 277 were excluded for the following reasons: 92 declined to participate, 79 had concomitant illnesses, 52 had a normal HVPG (less than 6 mm Hg), 21 could not tolerate the lowest dose of timolol, 15 had an HVPG of less than 10 mm Hg and non–biopsy-proven cirrhosis, 6 were lost to follow-up, 4 were consuming alcohol during the titration phase, 4 were receiving treatment with interferon or phlebotomy, 2 had primary biliary cirrhosis, and in 2, efforts to measure the HVPG were unsuccessful.

TITRATION OF THE DOSE

The dose of timolol (or placebo) to be used during the study was determined for each patient before randomization during a titration period in which open-label timolol was administered orally. The starting dose of timolol was 5 mg per day and was increased by 5 mg every three days until one of the following occurred: the resting heart rate was reduced by 25 percent from the baseline value, the resting heart rate fell below 55 beats per minute, a daily dose of 80 mg of timolol was reached, or the patient could not tolerate a further increase in the dose.

RANDOMIZATION

After the titration period, patients were randomly assigned to receive timolol or an identical-appearing placebo tablet. The randomization code was generated by computer for each participating center. Patients were stratified according to the cause of cirrhosis (alcoholic vs. nonalcoholic) and baseline HVPG (less than 10 mm Hg vs. 10 mm Hg or more). An alcoholic cause was defined as a long-standing history of alcohol ingestion exceeding 60 g per day. In patients with a dual alcoholic and viral cause, the classification of cirrhosis was based on the clinical and histologic findings.

FOLLOW-UP

Patients were assessed clinically at baseline, one and three months after randomization, and every three months thereafter. At each visit, the heart rate, pill count, occurrence of adverse events, and alcohol consumption were determined and blood was obtained for hematologic and biochemical measurements. To maintain study blinding, the patient's

Table 1. Baseline Characteristics of the Patients.*		
Characteristic	Timolol Group (N=108)	Placebo Group (N=105)
Age — yr	46±11	44±11
Male sex — no. (%)	70 (65)	56 (53)
Race or ethnic group — no. (%)		
White	100 (93)	98 (93)
Black	3 (3)	1 (1)
Latin-American	3 (3)	2 (2)
Indian	2 (2)	3 (3)
Mideastern or Arabian	0	1 (1)
Cause of cirrhosis — no. (%)		
Alcoholic†	26 (24)	25 (24)
Nonalcoholic	82 (76)	80 (76)
HCV	67 (62)	67 (64)
HBV	6 (6)	2 (2)
Cryptogenic	5 (5)	5 (5)
Other	4 (4)	6 (6)
Anti-HCV positivity — no. (%)	70 (65)	74 (70)
Child–Pugh score‡	5.4±0.7	5.4±0.8
Child–Pugh class — no. (%)		
A	98 (91)	91 (87)
B	10 (9)	14 (13)
Mean blood pressure — mm Hg	94±10	93±12
Heart rate — beats/min	75±11	74±10
Hemoglobin — g/dl	13.8±1.5	13.5±1.7
White-cell count — ×10⁻³/mm³	5.7±2.8	5.7±2.1
Platelet count — ×10⁻³/mm³	122±72	119±46
Total bilirubin — mg/dl	1.2±0.7	1.12±0.8
Albumin — g/dl	3.9±0.5	3.9±0.5
Prothrombin time — INR	1.34±2.53	1.34±2.52
Aspartate aminotransferase — U/liter	93±74	89±59
Alanine aminotransferase — U/liter	106±101	105±96
Alkaline phosphatase — U/liter	138±70	153±97
Serum sodium — mmol/iter	140±3	140±4
Blood urea nitrogen — mg/dl	14±8	15±10
Creatinine — mg/dl	0.9±0.2	0.9±0.2
HVPG — mm Hg	11.7±4.3	11.7±4.1
HVPG ≥10 mm Hg — no. (%)	67 (62)	67 (64)
Median follow-up — mo	52.7	57.9

* Plus–minus values are means ±SD. There were no significant differences between groups. Race or ethnic group was self-reported. To convert values for bilirubin to micromoles per liter, multiply by 17.1. To convert values for blood urea nitrogen to micromoles per liter, multiply by 0.357. To convert values for creatinine to micromoles per liter, multiply by 88.4. HCV denotes hepatitis C virus, HBV hepatitis B virus, and INR international normalized ratio.
† The majority (37 of 51 [73 percent]) had been abstinent from alcohol for more than one month; 5 others had evidence of mild alcoholic hepatitis at randomization (2 in the timolol group and 3 in the placebo group).
‡ The Child–Pugh score can range from 5 to 15, with higher scores indicating more severe liver disease.

heart rate was measured by the study nurse and not by the investigators. At baseline and every year thereafter, upper endoscopy was performed and HVPG was measured as described elsewhere.[5] According to standard practice at the time, no patient received antiviral therapy during the study.

END POINTS

The primary end points were the development of varices or variceal hemorrhage as identified unanimously at endoscopy by two staff endoscopists who were present during the entire procedure and who evaluated the procedure independently. Varices were defined by the presence of one of the following: large varices (at least 5 mm); small varices (less than 5 mm), confirmed by endoscopy 6 months later; small varices (less than 5 mm) on one endoscopy, with the patient's declining to undergo comfirmatory endoscopy or an inability to perform confirmatory endoscopy in the subsequent 12 months; or gastric varices confirmed by endoscopic ultrasonography. Variceal hemorrhage was defined as any hematemesis or melena in a patient in whom endoscopy showed active bleeding from an esophageal or gastric varix, an esophageal or gastric varix with an adherent clot, or varices but no other source of bleeding. In addition, acute, clinically significant bleeding as a result of portal hypertensive gastropathy (defined by the need for a 2-unit transfusion, a 6-point drop in the hematocrit, or a drop of more than 20 mm Hg in systolic blood pressure with a change in the patient's posture) was considered a primary end point.

Secondary end points were the development of ascites or encephalopathy, liver transplantation, or death. Data collection was terminated and treatment was considered to have failed when a patient reached the primary end point, underwent liver transplantation, or died.

ADVERSE EVENTS

An adverse event was any event that required a diagnostic or therapeutic intervention. All adverse events, regardless of their possible association with the disease or study treatment, were recorded. An adverse event was judged severe if it was considered to endanger the health or safety of the patient.

DATA AND SAFETY MONITORING BOARD

Members of a data and safety monitoring board were appointed by the National Institute of Diabetes and Digestive and Kidney Diseases and met ev-

ery six months to review the progress of the study and accumulated data. According to the protocol, one interim analysis was performed on October 26, 2000, after all patients had been enrolled. At that time, the data and safety monitoring board was empowered to recommend termination of the study on the basis of concern about safety or in the presence of sufficient evidence to indicate that timolol was statistically superior to placebo. The board voted unanimously to recommend continuation of the trial.

STATISTICAL ANALYSIS

We estimated that treatment with timolol would reduce the four-year cumulative probability of varices from 50 percent (the rate without treatment)[6,7] to 30 percent, given a statistical power of 80 percent to detect an absolute difference of 20 percent between the placebo and timolol groups at a two-sided alpha level of 0.05. We estimated that the study would require 193 patients, and we then increased this amount by 10 percent to account for the loss of patients to follow-up, yielding a total of 212 patients.

All analyses were conducted according to the intention-to-treat principle. Qualitative variables were compared by means of Fisher's exact test. Wilcoxon's rank-sum test was used to compare continuous variables or ordinal data. Actuarial probabilities were calculated according to the Kaplan–Meier method and compared with use of the log-rank test. Data were censored when the primary end point was reached, at the time of transplantation or death, or at the time of the last visit, whichever occurred first. A Cox proportional-hazards model was used to identify the variables that best explained the variability in the rates of primary end points, treatment failure, and survival. Calculations were performed with the use of the SAS statistical software package.

RESULTS

A total of 213 patients underwent randomization: 108 were assigned to receive timolol, and 105 to receive placebo (110 at the Barcelona center, 52 at the Connecticut center, 26 at the London center, and 25 at the Boston center). The median time from screening endoscopy to randomization was 29 days (range, 8 to 105). As shown in Table 1, the baseline characteristics were similar in the two groups. There were no significant differences between groups in the

proportion of patients with alcohol-induced cirrhosis or in the HVPG. The median Child–Pugh score was 5 (range, 5 to 9; scores can range from 5 to 15, with higher scores indicating more severe liver disease). The median HVPG was 11 mm Hg (range, 6 to 25), with 63 percent of the patients having an HVPG of at least 10 mm Hg. The median duration of follow-up was 54.9 months (range, 0 to 99.4).

The median daily dose of timolol was 10.8 mg

Table 2. Rates of Primary and Secondary End Points and Treatment Failure.

Variable	Timolol Group (N=108)	Placebo Group (N=105)	P Value
	no./total no. (%)		
Primary end point*	42/108 (39)	42/105 (40)	0.89
Large varices	4	4	
Confirmed small varices	27	30	
Unconfirmed small varices	8	5	
Variceal hemorrhage	2	3	
Hemorrhage from portal hypertensive gastropathy	1	0	
Secondary end point†	22/66 (33)	22/63 (35)	1.00
Ascites	4	6	
Death	3	2	
Hepatic encephalopathy	3	2	
Transplantation	1	0	
Death	0	1	
Ascites and encephalopathy	6	5	
Transplantation	1	0	
Death	5	5	
Transplantation	7‡	2§	
Death	10¶	15‖	
Treatment failure**	59/108 (55)	59/105 (56)	0.89

* No patient had isolated gastric varices as a primary end point. Among the patients in whom esophageal varices developed, five (four in the timolol group and one in the placebo group) had concomitant gastric varices (three had junctional and two had fundal varices).
† The total number in each group reflects the number of patients who did not reach a primary end point (66 in the timolol group and 63 in the placebo group).
‡ The reasons for transplantation were hepatocellular carcinoma in four patients, decompensated cirrhosis in two patients, and acute-on-chronic liver failure in one patient.
§ In both patients, the reason for transplantation was hepatocellular carcinoma.
¶ Four deaths were related to infection followed by renal or liver dysfunction, one was due to hepatocellular carcinoma, and five were unrelated to liver disease. Ascites, encephalopathy, or both developed in 8 of the 10 patients who died.
‖ Six deaths were related to infection followed by renal dysfunction, three were due to hepatocellular carcinoma, two were due to liver failure, and four were unrelated to liver disease. Ascites, encephalopathy, or both developed in 8 of the 15 patients who died.
** Treatment failure was defined by the occurrence of the primary end point (varices and variceal hemorrhage), transplantation, or death.

(range, 1.25 to 80.0) in the timolol group, and the median daily dose of the timolol placebo was 12.9 mg (range, 1.25 to 80.0) in the placebo group (according to titration). The dose had to be reduced in 29 patients (26 in the timolol group vs. 3 in the placebo group, P<0.001), and the study medication was withdrawn prematurely in 46 patients (25 in the timolol group vs. 21 in the placebo group, P=0.62).

Adherence to treatment was considered adequate if the pill count showed more than 70 percent adherence; this degree of adherence was achieved in 86 patients in the timolol group (80 percent) and 88 patients in the placebo group (84 percent).

END POINTS

The rates of the primary and secondary end points and treatment failure are shown in Table 2. A total of 84 patients reached the primary end point of varices or variceal bleeding: 42 of 108 patients in the timolol group and 42 of 105 patients in the placebo group (39 percent vs. 40 percent, P=0.89) (Table 2 and Fig. 1). The rates of the primary end point (both overall and for the timolol group) did not differ significantly when patients who had a reduction in the dose or stopped treatment were compared with those who did not have a reduction in the dose or discontinue treatment (data not shown). Hepatocellular carcinoma, which was not considered an end point of the study, occurred in eight patients in the timolol group and six patients in the placebo group.

Figure 1. Kaplan–Meier Estimates of the Percentages of Patients Who Did Not Reach the Primary End Point of Varices or Variceal Bleeding.

Cumulative percentages of patients who did not reach the primary end point at 12, 24, 36, and 60 months were 91 percent, 86 percent, 79 percent, and 60 percent, respectively, in the timolol group and 97 percent, 82 percent, 78 percent, and 57 percent, respectively, in the placebo group.

A comparison of the 84 patients who reached the primary end point with the 129 patients who did not reach the primary end point revealed that the following baseline variables differed at a P value of less than 0.1: the Child–Pugh score, the white-cell count, the aspartate aminotransferase level, the alanine aminotransferase level, and the HVPG. On Cox regression analysis, a baseline HVPG of 10 mm Hg or more (P=0.005) and an elevated aspartate aminotransferase level (P=0.007) were independently predictive of reaching the primary end point.

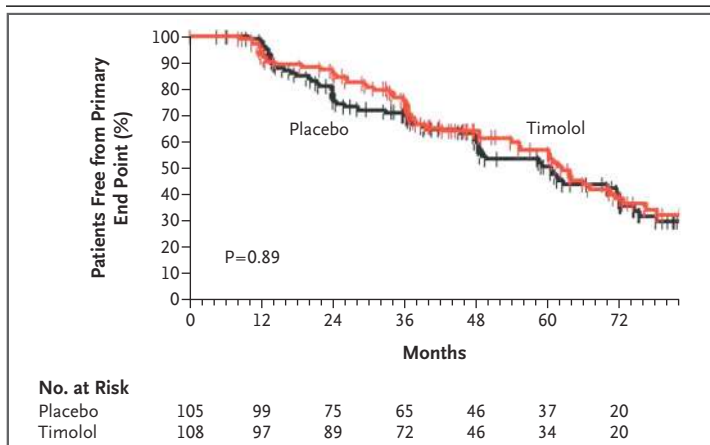### ADVERSE EVENTS

The incidence of moderate or severe adverse events was higher in the timolol group than in the placebo group (48 percent [52 patients] vs. 32 percent [34 patients], P=0.02). Serious adverse events considered probably related to study medication occurred in 20 patients (18 percent) in the timolol group (7 had bradycardia, as defined by a heart rate of less than 50 beats per minute; 5 had severe fatigue; 4 had wheezing or shortness of breath, 2 had syncope; and 1 each had intermittent claudication and impotence) and in 6 patients (6 percent) in the placebo group (1 each had impotence, hypotension, depression, heart failure, nodal rhythm, and bronchospasm) (P=0.006). None of the complications were fatal.

HEMODYNAMICS

Except at baseline, the heart rate was significantly lower in the timolol group than in the placebo group throughout the study (Fig. 2A). The average reduction in the heart rate from baseline was 17 percent in the timolol group. Conversely, the HVPG did not differ significantly between groups during the study (Fig. 2B).

At baseline, an HVPG of 10 mm Hg or more was associated with a significantly higher incidence of the primary end point, as shown in Figure 3A. HVPG measurements were repeated at one year in 154 patients (72 in the timolol group and 82 in the placebo group). As compared with baseline values, the HVPG decreased by a median of 1.45 mm Hg among patients in the timolol group, as compared with a decrease of only 0.5 mm Hg among patients in the placebo group (P=0.07); the decrease in the latter group was due solely to a drop in wedge pressure. Reductions in the HVPG of more than 10 percent (Fig. 3B), more than 15 percent, and more than 20 percent were all associated with a significantly lower incidence of the primary end point. More important, a decrease in the HVPG of more

than 10 percent, more than 15 percent, or more than 20 percent from baseline occurred more frequently in the timolol group (53 percent, 43 percent, and 33 percent, respectively) than in the placebo group (38 percent, 24 percent, and 19 percent, respectively), and these differences were significant (P=0.04, P=0.01, and P=0.04, respectively). Conversely, an increase in the HVPG by more than 10 percent also correlated with an increased likelihood of reaching the end point (Fig. 3C). However, there were no significant differences between groups in the increases in HVPG.
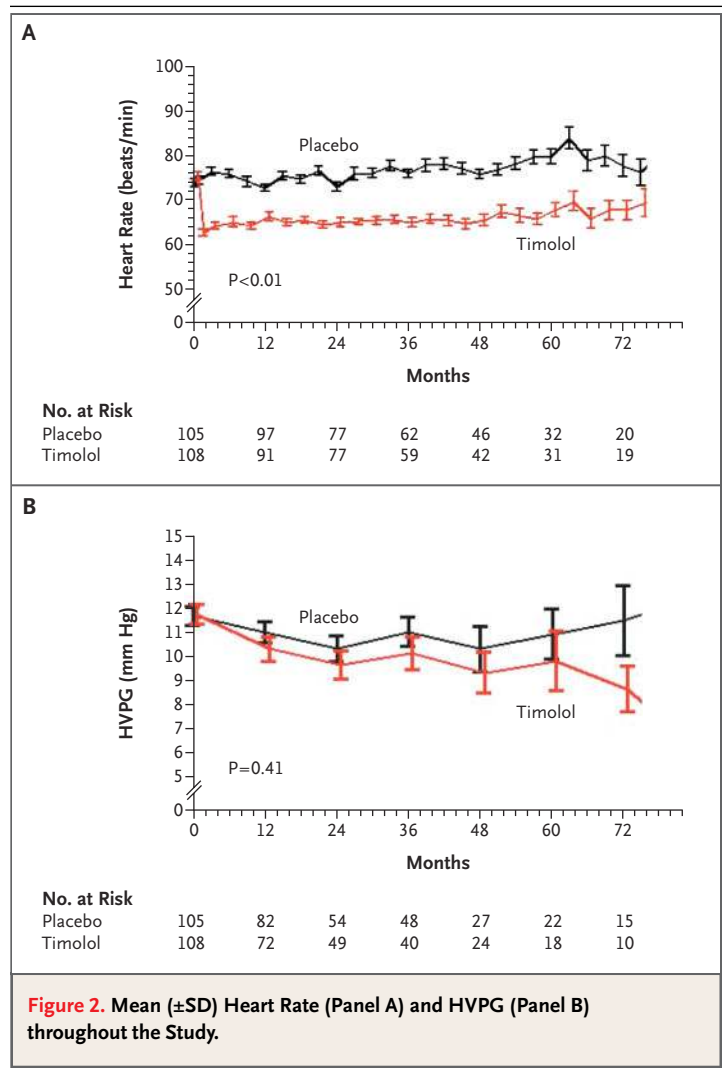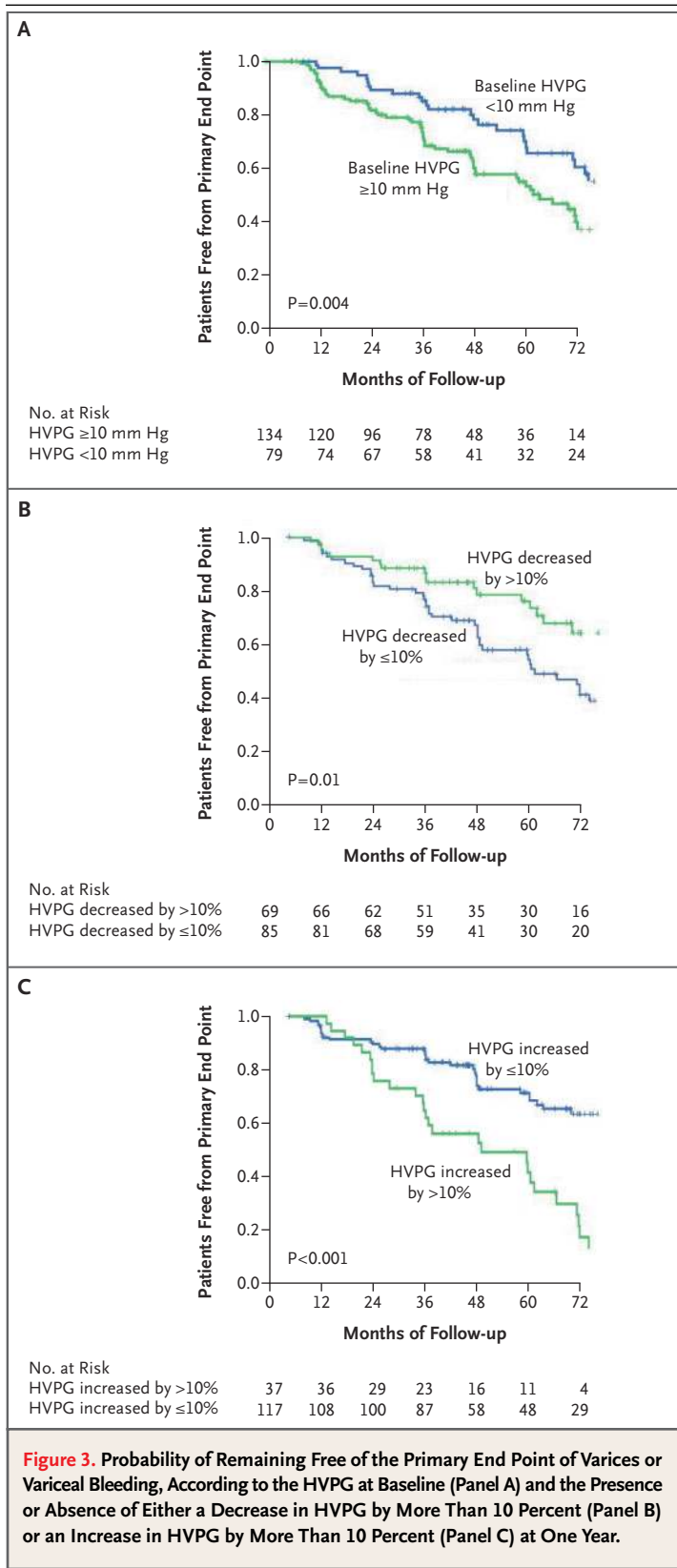
DISCUSSION

In this placebo-controlled study, treatment with a nonselective beta-blocker, timolol, did not prevent gastroesophageal varices in unselected patients with cirrhosis and portal hypertension and was associated with an increased number of adverse effects. A previous French study of the prevention of varices showed that, in patients without varices or with small varices, the development of large varices was more frequent among propranolol-treated patients than among patients who received placebo. Most of the patients had small varices, and significant differences were confined to this subgroup of patients.[8] In contrast, a placebo-controlled study that consisted of patients with small varices found a lower rate of variceal enlargement in patients treated with nadolol.[9]

We used timolol, a potent nonselective beta-blocker,[10] and as shown in patients with essential hypertension,[11] once-daily dosing was sufficient to maintain the reduction in heart rate for at least 24 hours. Moreover, the fact that timolol has a higher affinity for both β_1- and, particularly, β_2-adrenergic receptors than do propranolol and nadolol[10,12] is important, since β_2-adrenergic–receptor blockade is an important target in the reduction of portal pressure.[2] In a study of acute effects, timolol decreased HVPG as effectively as did propranolol or nadolol.[13] However, there are differences in the acute and chronic portal-pressure–reducing effects of beta-blockers,[14,15] which have been ascribed to differences in receptor blockade (β_1-adrenergic receptors are involved in the acute effect and β_2-adrenergic receptors in the chronic effect).[15] Our negative results may have been partially due to the inclusion of patients with an early stage of cirrhosis and thus a milder splanchnic and systemic hyperdynamic circulatory state, a major factor in the maintenance of portal hypertension and the main target of the action of beta-blockers.

The average decrease in heart rate in the timolol group was 17 percent. This reduction is smaller than the range of 20 to 26 percent (median, 24 percent) reported in studies of beta-blockers in the primary prophylaxis of variceal hemorrhage[16-24] and is probably due to the lower baseline heart rate (median, 73 beats per minute) in our study than in primary-prophylaxis studies of patients with varices (median, 80 beats per minute)[9,17-25] or secondary-prophylaxis studies of patients with varices (median, 84 beats per minute).[26-29] However, the absolute heart rate achieved is a better indicator of beta-blockade than the percent reduction in heart rate,[30] and the absolute heart rate in our study during timolol therapy (62 beats per minute) was similar

Figure 2. Mean (±SD) Heart Rate (Panel A) and HVPG (Panel B) throughout the Study.

Figure 3. Probability of Remaining Free of the Primary End Point of Varices or Variceal Bleeding, According to the HVPG at Baseline (Panel A) and the Presence or Absence of Either a Decrease in HVPG by More Than 10 Percent (Panel B) or an Increase in HVPG by More Than 10 Percent (Panel C) at One Year.

to the median heart rate of 60 beats per minute among patients receiving beta-blockers in previous studies.[17-24]

The lack of an overall significant change in the HVPG may partly explain our negative results. Although it is possible that positive results could have been obtained if the dose of timolol had been higher, drug intolerance limited our ability to increase the dose further in this group of patients with compensated cirrhosis, most of whom were reluctant to tolerate even minimal side effects.

A major finding of our study was the effect of baseline HVPG on outcomes. The rate of the primary end point was significantly lower among patients with a baseline HVPG of less than 10 mm Hg than among patients with a baseline HVPG of at least 10 mm Hg. This finding supports the definition of clinically significant portal hypertension as an HVPG of at least 10 mm Hg.[31] In fact, the baseline HVPG was the strongest independent predictor of the development of varices.

We confirmed the importance of lowering portal pressure shown in previous studies of patients with more advanced cirrhosis.[29,32-35] We found that reductions in the HVPG of more than 10 percent from baseline were related to a significant decrease in the rate of the primary end point. An important finding was that more patients in the timolol group than in the placebo group had these favorable HVPG responses, indicating that timolol had a beneficial effect, but one that was not sufficient to tip the balance in favor of beta-blockers. Conversely, we also found that increases in portal pressure were associated with the development of varices, although timolol apparently had no ability to prevent this increase in HVPG.

In conclusion, even though the role of nonselective beta-blockers in preventing variceal hemorrhage in patients who already have varices is well established, we found that nonselective beta-adrenergic blockers did not prevent varices in patients with cirrhosis and portal hypertension. The use of beta-blockers cannot be widely recommended in this population because of its association with an increased incidence of serious side effects. However, even in this population of patients with compensated cirrhosis, we have confirmed the predictive value of baseline HVPG levels and of a subsequent reduction in the HVPG by more than 10 percent, the latter of which should be the goal in the pharmacologic prevention of gastroesophageal varices.

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